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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 87754-7500

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

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Application Number	Filed
10/644,687	August 19, 2003

First Named Inventor: Haim AVIV

Art Unit	Examiner
1626	Taofiq A. Solola

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☐ attorney or agent of record. Registration number _____
- ☒ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34: 57,004

Signature

Evert F. Uy (For: Allan A. Fanucci, Reg. No. 30.256)
Typed or printed name

202-282-5793
Telephone number

March 30, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Haim AVIV et al.

Confirmation No.: 6729

Application No.: 10/644,687

Group Art Unit: 1626

Filing Date: August 19, 2003

Examiner: Taofiq A. Solola

For: HIGH ENANTIOMERIC PURITY DEXANABINOL FOR PHARMACEUTICAL COMPOSITIONS

Attorney Docket No.: 87754-7500

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicants request a panel review of the decision of the Examiner mailed December 5, 2005 rejecting claims 1-6 and 8-24.

The above-identified application is directed to the compound dexanabinol having the (3S,4S) configuration (HU-211) and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer (HU-210). The claims were rejected as anticipated by or obvious over U.S. Patent No. 5,284,867 to Kloog et al. ("Kloog"). The Examiner maintains that Kloog discloses the compound of the present invention, essentially free of the (3R, 4R) enantiomer.

Applicants stress that Kloog does not disclose or teach HU-211 having the (3S,4S) configuration and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer, as presently claimed. For this reason there can be no anticipation of the present claims. Kloog's HU-211 and the HU-211 claimed are significantly different compounds with different properties, which are attributable to the differences in enantiomeric purity. Kloog's HU-211 cannot obtain the recited purity level as exhibited by its different process of manufacture and inducement of side effects such as stereotypy, locomotor hyperactivity and tachycardia (Col. 5, lines 26-32).

To demonstrate unexpected results, Applicants have established that the presently claimed compounds with their higher purity level can be administered advantageously at higher doses, without causing deleterious side effects. Applicants have submitted a Declaration which included evidence supporting Applicants' position that the compound of Kloog is substantially different in its properties from the claimed compound. In particular, it was shown that the compound of Kloog caused a drastic drop in rectal temperature, almost totally inhibited spontaneous locomotion, and caused significant catalepsy, while the claimed compound did not exhibit any of these adverse effects.

Kloog does not teach the synthesis of HU-211. As there is no synthetic route disclosed in Kloog, it is understood that Kloog's HU-211 was prepared by Professor Raphael Mechoulam, a co-inventor in Kloog. Thus, the compound disclosed in Kloog is a sample that was prepared according to procedures known and used by Mechoulam. In this case, Applicants understand that the compound of Kloog was prepared according to the original synthetic procedure developed by Mechoulam.

The Examiner contends that the results presented in the Declaration are not a true side-by-side comparison, and insists that the Mechoulam sample described in the Declaration does not represent a true Kloog sample. This is incorrect. The Mechoulam sample was prepared according to a slightly modified but improved version of Mechoulam's original synthetic procedure. Indeed, the Mechoulam sample obtained by the modified procedure either corresponds to the Kloog sample or is even superior to the Kloog sample with respect to enantiomeric purity. Applicants therefore submit that the Mechoulam sample is comparable to and does represent the Kloog sample.

In particular, the Mechoulam sample was tested and found to contain 91.1% HU-211 and 0.26% HU-210, yielding an enantiomeric excess of 99.4%, which is much less than the at least 99.90% claimed. Consequently, Kloog cannot anticipate the claimed invention because it does not teach or disclose each and every feature in the claims.

The Examiner asserts that the difference between 99.4% enantiomeric excess and 99.9% enantiomeric excess is within experimental error and/or design. This is also incorrect. Kloog does not disclose or suggest any importance of achieving 99.90% enantiomeric excess and does not disclose a process for obtaining such excess. While 99.4% and 99.9% appear at first glance to be very close in value, these values refer to calculated enantiomeric excess percentages

that do not reflect the original absolute amounts of the individual enantiomers. Enantiomeric excess is different from purity in general and is derived from the following formula:

percent enantiomeric excess = 100 x ([HU-211] - [HU-210])/([HU-211] + [HU-210])

wherein the concentration of the enantiomers is separately determined by HPLC and expressed as percent by weight.

For example, the content of HU-211 in the Mechoulam sample was found to be 91.1%, while that in a sample according to the present invention was found to be 98.8%. This is a difference of more than 7.5%. The content of HU-210 in the Mechoulam sample at 0.26% is more than 10 times that in the sample according to the present invention. These differences in content are not attributable to experimental variation, and are certainly more than a person of skill in the art would accept from validated analytical methods.

As described previously, this distinction results in significantly different biological properties of HU-211. Animals that were administered the Mechoulam sample displayed dramatic hypothermia, catalepsy, and locomotor inhibition. In contrast, animals that were treated with the sample according to the present invention did not exhibit any of these adverse side effects. The presence of only 0.26% HU-210 (a seemingly small amount) is enough to cause these serious side effects.

The Mechoulam sample and consequently, Kloog, simply do not provide HU-211 with an enantiomeric excess of at least 99.90%. This overcomes any allegation of anticipation. Furthermore, the present compounds unexpectedly avoid the side effects of the Kloog compounds. Accordingly, because Kloog does not teach or suggest the compounds of the present claims, nor the attendant benefits resulting from the administration of such compounds, no *prima facie* case of obviousness has been made on the record, and this rejection should also be withdrawn. In view of the record, it is believed that the claims should be allowed at this time.

Respectfully submitted,

Date: 3/31/06

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